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The Mode of Action of Oral Contraceptives

THOUGH MODERN SCIENTIFIC techniques have improved previous contraceptive practices, making them more accurate and safe, they have so far produced little that is new. Even oral contraceptives have their precursors for many herbs and roots and plants and minerals have been used orally as well as locally for hundreds of years, some of them containing oestrogens which could have had a contraceptive effect. In the last nine years while oral contraceptives, which act by inhibiting ovulation, have become a practical reality, there has also been an impetus to research into all the various mechanisms involved in fertilization and contraception, so that it seems likely that other oral contraceptives with a different mode of action will become available before very long. Inhibition of ovulation is already possible with non-steroidal anti-gonadotrophic substances and with agents introducing central neural blockade; other drugs are known to interfere with implantation and with fertilization, while in the relentless pursuit for oral contraceptives for men many groups of oral compounds have been found which are anti-spermatogenic.

Some workers, notably in the U.S.A., have already used drugs which are anti-spermatogenic in the human male, but so far no compound has been found to be effective without unfortunate side-effects. The nitrofurans are not tolerated in the human in the dosage required, the bis (dichloracetyl) diamines cannot be taken with alcohol because of an antabuse effect; the dinitrophenols are toxic in dogs and monkeys and do not seem likely to be useful though other compounds in the series are being examined. These all have the same type of effect, they function at the stage of primary spermatocytes and testicular recovery is prompt after medication is stopped: no mutagenic effect has been shown to occur and there is apparently no suppression of gonadotrophic hormone. Because of the site of action, however, one of the disadvantages of these compounds is that they take some fifty days to be fully effective after treatment is begun and a similar time after cessation of treatment for normal fertility to be restored. There is therefore no male pill yet ready for clinical evaluation. It is also possible to affect spermatogenesis indirectly through suppression of gonadotrophic secretion by a variety of steroidal agents, all of which would have a more immediate effect on fertility but much basic research is required before these will be ready for even preliminary clinical trial.

History of the Development of Present Day Oral Contraceptives

The ovulation inhibiting effect of the corpus luteum has been known since the beginning of this century. Since 1921 it has been known that progesterone could inhibit ovulation in the experimental animal and after its isolation in 1934 it was soon shown that not only progesterone but testosterone and oestrogen could inhibit ovulation through inhibition of pituitary gonadotrophin. However, until 1954 these steroids were not of practical value as anti-fertility agents in humans for various reasons: for example, progesterone is inactive by mouth and daily administration by injection quite impractical, while androgens have to be administered in large doses at which they produce undesirable side-effects; oestrogens were considered to be unreliable on continued therapy, and it was feared that the continued administration of oestrogen would give troublesome menstrual bleeding and excessive endometrial proliferation; then

too there has always been a widespread but probably unfounded fear of the carcenogenicity of oestrogens. The breakthrough came in 1954 when Djerassi *et al.* using a new chemical technique synthesized different steroids (the 19-nor testosterone derivatives) which were shown to be not only very much more active than progesterone but also active on oral administration. A great many such progestational steroids have since been tested and those used as oral contraceptives are mainly 19-nor testosterone derivatives but also 17-acetoxy progesterone derivatives.

Chemistry and Pharmacology

Testosterone or 19-Nor Testosterone Derivatives

Most of the oral progestagens used in oral contraceptive products belong to this group; these derivatives lack the side chain structure of progesterone previously thought to be necessary for progestational activity (the angular methyl group and therefore carbon atom 19 between rings A and B). They include norethisterone, norethynodrel, lynestrenol and ethylnodiol diacetate, which are all close structural relatives. These compounds are oestrogenic to a varying degree, probably because they are partly metabolized to oestrogenic compounds. They are highly potent ovulation inhibitors, are very active in the postponement of menstruation assay, and produce progestational changes in the oestrogen-primed endometrium. They also have a marked haemostatic effect on uterine bleeding of endocrine origin.

17-Acetoxy Progesterone Derivatives

These derivatives are produced either by esterification of the 17-alpha hydroxyl group or by esterification plus the introduction of other substituents, for example the halogen or methyl group at the position 6. They are less powerful ovulation inhibitors than the others, they have no inherent oestrogenicity and they are not such efficient haemostatics, though some are more powerful progestagens with regard to maintenance of the endometrium.

Progestational compounds in both these groups administered in the oral contraceptive regime—that is one tablet daily from day 5 to 25 of the menstrual cycle suppress the endogenous ovarian production of progesterone and oestrogen. They appear to be even more potent combined with an oestrogen (and vice versa) so that combining progestagen and oestrogen enables each to be effective in smaller doses than when given alone. For this reason it has been found worthwhile to combine the progestagen with some oestrogen not only for oral contraceptive purposes but also for gynaecological purposes, and this has enabled the dose required to be much lower than was at first thought to be necessary. Furthermore those progestagens which have no inherent oestrogenicity require the addition of oestrogen to support the endometrium and to give better cycle control. Since progestagens are more expensive than oestrogens this combined tablet reduces the cost while increasing the efficiency and lowering the incidence of some side-effects.

Present oral contraceptives therefore are a combination of one of seven progestational steroids and one of two oestrogens—either ethinyl oestradiol or ethinyl oestradiol 3-methyl ether (mestranol). Mestranol was the first to be used in this connection, as it was a contaminant, being a precursor in the synthesis of norethynodrel. Later ethinyl oestradiol was used and it has the advantage that it has been in clinical use for nearly thirty years.

The optimal dose has first to be assessed, to find an adequate dose from the point of view of over-all efficiency and to find the optimal balance of the two hormones. The most important criteria apart from clinical effectiveness, which is of course of paramount importance, appear to be a low incidence in all cycles of breakthrough bleeding, with the minimum of oestrogenic/progestagenic side effects. Though other studies hold promise for the future, so far there are no short cuts to clinical evaluation. It appears that with some progestagens the proportion of progestagen/oestrogen is more important than with others to fulfil these criteria.

Sequential Therapy

As will be discussed later, the dose of oestrogen in most of the present oral contraceptive tablets is in itself sufficient to inhibit ovulation and some investigators believe that the oestrogen is wholly responsible for the efficacy. A more

recent development in oral contraception using oestrogen only to inhibit ovulation with some progestagen added for the last few days is of much interest. It is of course cheaper, it more closely mimics the normal menstrual cycle and gives a more physiological endometrium and cervical mucus and offers a more normal cyclic variation for women who feel that the constant dosage of the normal oral contraceptive regime does not suit them. The side effects with sequential therapy are similar to the best of the combined tablets, though there are one or two differences—for example there is less breast discomfort, but there is increased menstrual loss in 25 per cent of cases. Present experience however suggests that this is not such an efficient method, though investigators disagree as to the reason for this. This regime is therefore still in the experimental stage. The consensus of opinion in this country at the time of writing is that the biggest advantage of oral contraceptives is the increased efficiency and that there is no point in introducing an oral contraceptive which is less efficient than the established ones.

Metabolism

Little is known of the metabolism of the oral contraceptive products and only norethisterone and norethynodrel have been studied in any detail. Using radio-active norethisterone and norethynodrel Layne *et al.* showed that at least 70 per cent of the administered dose was absorbed, that the excretion was fairly rapid, most of the radio-activity appearing in the urine or faeces within four days of administering the compound. Some of the norethynodrel administered was metabolised to norethisterone, most of the metabolytes appeared to retain ethinyl side chain and the hydroxyl group at position 17 of the molecule. Thus what little evidence there is suggests that the progestational compounds are readily and quickly absorbed after oral administration and that after stopping treatment they are inactivated and excreted rapidly.

A great deal of study has gone into the experimental trials with these steroids. The combined oestrogen/progestagen oral contraceptives have proved beyond doubt to be the most effective we have ever had and to be acceptable to many couples who dislike conventional contraceptive measures, or who have found them insufficiently reliable. Since they are hormones, however, they have effects other than inhibition of ovulation, so that the short-term and perhaps even more important the long-term effects of the use of these potent hormones on the endocrines and on biochemical body functions is extremely important and has raised many anxieties. The more important of these will be considered:

Effect on the Pituitary

Holmes and Mandl drew attention to the pituitary enlargement found in adult rats treated over long periods with norethynodrel and found to be due mainly to an increase in chromophobe tissue. Information on the effect of human pituitary morphology is of course scanty, but no cases of pituitary tumour have been reported during extensive clinical experience of nearly nine years. There is very convincing evidence too that after cessation of treatment normal menstrual function and hormone output are quickly restored, the rate of fertility is increased and the pregnancies which result are normal, thus demonstrating that the alteration in pituitary and ovarian endocrine activity and interrelationships produced by these ovulation inhibitors is promptly reversible even after some years of cyclic treatment.

Effect on the Ovary

(*a*) *Morphology*. The ovaries appear to be immediately altered in appearance by oral contraceptive medication; where laparotomy and culdoscopy have been undertaken even after only one cycle of medication, the gross appearance is reported to be that of an atrophic or menopausal-looking ovary. This is apparently immediately reversible on stopping medication even after six or seven years of treatment. Data on human ovaries is not very large, but Rock, Garcia, Ostergard, Laweryns and Ferin have all reported on ovarian biopsies from patients under treatment and following treatment, and they have found an absence of fresh corpora lutea, and absence of functioning or recent involutive corpora lutea, but otherwise normal follicles and normal stroma.

(*b*) *Function*. Many workers have shown that the normal luteal phase increase in the urinary

excretion of pregnanediol does not occur in patients treated with oral contraceptives from cycle day 5 to 25, and it has been inferred from this that ovulation is inhibited. Investigators who have undertaken hormone assays of patients on such therapy are agreed that ovarian inhibition is the rule, with suppression of oestrogens, though Shearman found one patient with a high atypical oestrogen excretion pattern which required a double dose to reduce it. More recently it has been shown with random sample cycles of patients on long-term treatment that occasional breakthrough ovulation does occur, so that ovarian escape from inhibition occurs during treatment. It certainly seems from all this evidence that the ovary, though dramatically affected by all this medication, recovers on cessation of treatment, and even escapes occasionally during continued therapy.

Effect on Vaginal Cytology

Administration of combined progestagen/oestrogen oral contraceptives causes a reduction in the vaginal cornification index. This occurs to a variable degree with different compounds and is probably a question of how much the anti-oestrogenic action of the progestagen is neutralized by the amount of endogenous plus exogenous oestrogen. In sequential therapy, of course, the cornification index rises earlier in the cycle than normal and remains rather steadily at normal level until the progestagen is added, when it is somewhat depressed. There are rarely any real progestagenic changes in vaginal cytology with 15/5 sequential methods, and very little where progestagen is added for ten days, as in the 11/10 regime.

Effect on the Endometrium

The characteristic distortion of the endometrium produced by combined oral contraceptives has been described by several investigators, Rice-Wray, Jackson, and others. The endometrium never becomes as thick as in a normal cycle and endometrial biopsies can be difficult to procure after a few months of therapy. Administering progestagen with the oestrogen from day 5 of the cycle prevents the normal oestrogenic priming or proliferation of the endometrium, so that though early proliferative changes do begin, there is much less marked glandular development than normal; the progestagen causes basal vaccuoles and stromal oedema to appear early, followed by glandular regression and abundant fibrillary stroma. Later there is marked stromal oedema and a predecidual effect until the onset of withdrawal bleeding.

With sequential therapy the endometrium is subjected to unopposed oestrogen for the first ten to fifteen days of treatment, so that there are fully developed proliferative changes which only subside slightly when the progestagen is added and the progestagenic effects found at the end of a normal menstrual cycle never develop.

Effect on the Cervical Mucus

The administration of progestagen from day 5 of the cycle appears to prevent the normal effects of oestrogen on the cervical mucus. Normal ovulatory mucus is rarely found, though there is an occasional patient with clear, copious mucus and normal sperm penetration. Mostly the secretions are viscous and scanty, and sperms if present are sluggish and few in number. With sequential therapy, of course, as would be expected, a normal ovulatory cervical mucus is found with normal sperm penetration and motility.

Mode of Action of Oral Contraceptives

(*a*) *Animals.* In animals the balance of evidence is in favour of the view that progestational agents act by inhibiting the pituitary rather than by exerting a direct effect on the ovary. Thus mating-induced ovulation in the rabbit can be inhibited by pre-treating the animal with various progestagens; however, if the treated animals are injected with gonadotrophin ovulation occurs, so that the ovary is still capable of responding to gonadotrophic stimulation. In the rat which ovulates spontaneously, similar results have shown that ovarian inhibition did not occur when gonadotrophins were administered to rats treated with norethynodrel. Experiments on parabiotic rats and mice also demonstrated an inhibitory effect of oral contraceptives on gonadotrophin secretion. While Nelson and Patinelli in 1960, suggested that luteinizing hormone might be inhibited by smaller amounts of steroid than are necessary for inhibition of follicle-stimulating hormone, other workers suggest that

though the predominant action of these steroids appears to be on the pituitary, the ovary may also be affected (corpora lutea smaller and luteinization less intense). It has been shown too that although treatment of rats with norethynodrel at a dose level sufficient to cause sterility would decrease ovarian function, it did not always block ovulation since ovaries in some of the treated animals contained corpora lutea. Holmes and Mandl (1962) in an excellent review of the literature, concluded that the weight of evidence in experimental animals favoured the view that the compounds acted by pituitary inhibition rather than by a direct effect on the ovary, though the point had not yet been definitely proved.

(*b*) *Humans*. The site of action in humans is not so easy to determine, for it is not possible with present assay methods to measure separately the follicle-stimulating hormone and luteinizing hormone, and it is recognized that ovulation could be inhibited by altering the balance of these two without altering total gonadotrophin levels. It has been shown that in post-menopausal patients the urinary excretion of human pituitary gonadotrophins is depressed during therapy; however, there are many indications that the effect of oral contraceptives on women of reproductive age is due to direct inhibition of ovarian activity and ovulation as judged by assays of oestrogens, pregnanediol and pregnanetriol in urine without affecting total gonadotrophic output. It has also been shown that the direct injection of 1mg. of crystalline progesterone or 0·05mg. of crystalline oestradiol under the tunica of the ovary in the early stage of the menstrual cycle can prevent ovulation and corpus luteum formation. It is not likely that such small doses act by way of the pituitary, since systemic injections at this level are ineffective. Contrary to these results however there are other workers who find diminished gonadotrophin excretion or inhibition of the peak of gonadotrophin excretion although the basal excretion was maintained, while even more recent results favour the possibility that these compounds act as specific inhibitors of LH.

There is also a conflict of opinion for methodological reasons as to whether the progestational steroids inhibit the ovarian response to exogenous gonadotrophins. Furthermore it is generally agreed that inhibition of ovulation can be effected by ethinyloestradiol or mestranol alone in the dosage used in present oral contraceptive tablet formulations and that this is caused by an inhibitory action on pituitary gonadotrophins. Whether therefore the progestational steroid also exerts pituitary inhibitory effect could be irrelevant, as the amount contained in oral contraceptive tablets is not in all cases sufficient to inhibit ovulation by itself. The picture is further complicated by the fact that the 19-nor steroids are partly metabolized into ethinyloestradiol, which in itself could be enough to account for the ovulation-inhibiting effect of some of these 19-nor steroids, though this is not true of the 17-acetoxyprogesterone derivatives. For these reasons, many people believe that oestrogen plays the dominant role in suppressing ovulation and this has led to the use of sequential therapy.

Contributory Factors. It has been recognized for some time that the antifertility action of the progestational steroids depends not only on ovulation inhibition but also on other factors, such as the effect on cervical mucus, which remains viscous and hostile to sperms throughout the cycle and by the alterations already described to the endometrium, which could well prevent implantation. Goldzieher first drew attention to the fact that although the effectiveness of these combined progestagen/oestrogen tablets was so high, an occasional breakthrough ovulation occurred in patients on long-term medication. He found a positive or doubtful pregnanediol elevation in 9 per cent of the cycles studied among his original series of patients on 10mg. Orthonovin, although no pregnancies occurred. More recently other investigators have confirmed this and have found ovulation in some 5 to 8 per cent of cycles. Despite this, the effectiveness of the method is undoubted. In trials under the auspices of the Council for the Investigation of Fertility Control in this country, the failure rate remains constant at around 0·74 pregnancies per 100 women years, and these are due largely to patient failures, despite the fact that the patients taking part missed at least one tablet in 4 per cent of all cycles. Further light has been shed on this by the more recent experience with the sequential method, which is

apparently less effective. In C.I.F.C. trials for example, the failure rate has been five pregnancies per 100 women years, with two of the formulations studied. It appears that again ovulation is inhibited in most cycles with the sequential method, but an occasional breakthrough ovulation occurs in later cycles as with combined methods. In the case of sequential therapy however, the more normal endometrium makes implantation and pregnancy possible. The writer suggests that when breakthrough ovulation occurs, the amount of progesterone secreted might be enough to produce the changes necessary for implantation in an endometrium which has been well-primed with oestrogen, as is the case in sequential therapy. As far as combined oral contraceptives are concerned, giving progestagen right from the start of therapy in conjunction with the oestrogen prevents the normal oestrogenic effect on the endometrium, preventing the endometrium therefore from responding to progesterone when breakthrough ovulation does occur, so that implantation is prevented.

Clinical Effects

In the early days of medication a few patients do have side effects which are related to the oestrogen/progestagen balance of the particular product, and these have been well documented. Though nausea was troublesome in the beginning the incidence is less now that the dosage is reduced and the anxiety about the method less. Occasional mastodynia, weight increase, cramps, headache, minor changes in libido and depression are complained of, but few of them cause patients to withdraw. After the first cycle or two the majority of patients have a sense of well-being resulting partly from the security which the method gives, partly from the absence of distasteful contraceptive measures, but also from the disappearance of pre-existing complaints such as dysmenorrhoea and premenstrual tension. The majority of women too have regular cycles with a decreased amount of menstrual loss even to the extent of occasional amenorrhoeic cycles. Occasionally breakthrough bleeding is a problem and calls for a change to a more progestagenic tablet.

The administration of oestrogens and progestagens alone and in combinations have some effect on various endocrine and metabolic processes. They have been shown to cause in some cases an increase in protein-bound iodine, in aldosterone secretion and in plasma cortisol. The effect on aldosterone secretion and metabolism is apparently related to both oestrogenic and progestagenic potency, while the effect on plasma cortisol is related almost entirely to the oestrogenic potency. In some instances, as would be expected, there is a decrease in the excretion of 17-keto steroids and 17-hydroxy steroids, for this is known to occur with oestrogen administration, but it has been shown that this does not affect the responsiveness to ACTH stimulation. Abnormal glucose tolerance curves have been found in some cases, particularly in women with a family history of diabetes—but the significance is yet to be assessed, for abnormal glucose tolerance has been found in from 10 per cent to 81 per cent of natural pregnancies, so that it could be a physiological response. This too is more likely to be associated with oestrogen than with progestagen administration. The possible hepatoxicity of steroids particularly those with an alkylated group at C-17 has been raised. In some cases serum transaminase levels and bromsulphthalein retention have been increased with patients on oral contraceptives; but it has also been shown that oestradiol and oestriol increase BSP, so that this again could be a physiological response and not a sign of liver damage. The possibility of foetal masculinization has been discounted at oral contraceptive dosage, and though some of these progestagens are mildly androgenic in laboratory animals, no virilization has been reported clinically. Concern has also been raised over a possible relationship between oral contraceptives and the occurrence of thrombo-phlebitis and pulmonary embolism, but a special committee set up by the F.P.A. concluded after careful study that on the basis of the available data there was no significant increase in the risk of thrombo-embolic disease from the use of oral contraceptives. Again, there are some minor changes in blood-clotting factors, but since there is at present no valid test for measuring the coagulability of the blood, the significance of these is not known.

It is quite clear then that these progestagen/oestrogen mixtures are responsible for many changes in many organs throughout the body, and it is hardly surprising that they have raised so many anxieties over possible harmful long-term effects and over upsetting the pituitary /ovarian and other endocrine relationships. These findings are difficult to assess for they are often similar to changes in normal pregnancy, and they could all be physiological responses which are no more important than the increase in gastric secretion which follows the ingestion of food. There obviously remains a great deal to be studied before we can be sure of the lack of long-term harmful effects; but while these could have a deleterious effect on thyroid, adrenals, the liver, etc., remarkably few cases of clinical abnormalities or dysfunction of these organs have been found with patients on oral contraceptives. The post-treatment increase in fertility however is the best proof of the integrity of the reproductive processes, so that their administration seems more like a physiological take-over of pituitary control by exogenously administered hormones rather than a disruption or interference.

All active drugs produce some side-effects and carry some potential risk, and the hazards of administration of any drug must be weighed against the benefit to the individual patient. In this connection we have to bear in mind the known risks connected with pregnancy particularly in women of high parity and the risks from criminal abortion as well as the unhappiness and mental stress which is often occasioned by the involuntary pregnancy. Though contraceptive measures have to be used on and off for thirty years in the life of the average fertile woman, it is quite unlikely that this method; important and revolutionary though it is, will be used for very many years; simpler less expensive methods involving much less in the way of medical supervision will be required to begin to solve world population problems.

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